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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE		
	Application Number	09/601,444
	Filing Date	January 4, 2001
	First Named Inventor	Esther H. Chang
	Group Art Unit	1632
	Examiner Name	Dave Trong NGUYEN
	Attorney Docket Number	2444-101
Title of the Invention: TARGETED LIPOSOME GENE DELIVERY		

DECLARATION

Assistant Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

I, Esther Chang, declare that:

1. I am the same Esther Chang named as an inventor on the above-referenced patent application.

2. I received a B.A. degree in biology from Fu Jen University in Taiwan in 1968 and a Ph.D. in microbiology from Southern Illinois University in 1974. From 1982-1994 I held the positions of Assistant Professor, Associate Professor, and then Professor in the Department of Pathology, Uniformed Services University of the Health Sciences in Bethesda, MD. I also was a Research Professor in their Department of Surgery and the Director of their Tumor Biology Program. From 1994-1996 I held the position of Professor of Surgery (Research), Division of Otolaryngology/Head and Neck Surgery in the Department of Surgery

at Stanford University Medical Center. Since 1996, I have held the position of Professor of Surgery (Consultant) there. I currently also hold the positions of Professor of Otolaryngology, Department of Otolaryngology/Head & Neck Surgery and Professor of Oncology and Otolaryngology, Departments of Oncology and Otolaryngology, at the Georgetown University Medical Center, Lombardi Cancer Center, and have held those positions since 1996 and 1999, respectively. A copy of my curriculum vitae is attached hereto.

3. I have read the Office Action issued by the U.S. Patent and Trademark Office on November 6, 2002, and understand the grounds of rejection set forth therein.

4. In one rejection the examiner asserted that the claims are not enabled because there is no evidentiary support from the application as filed to show that a person of skill in the art would have been able to make and use the claimed cationic liposome/ligand/therapeutic agent complex in the context of any gene therapy. He averred that a simple inhibition of a tumor in a murine model does not appear correlated to any therapeutic effect in a cancer gene therapy.

5. The examples presented in this application are far more substantive than "a simple inhibition of a tumor in a murine

model." In our application, we have presented multiple examples of the effectiveness of complexes of our invention in treating human xenografts in mice. The complexes thus were targeting human cancer cells in a live animal. The biochemistry among mammals is highly similar. There are many intimately shared pathways between mice and humans, and the use of xenograft-induced mice is, in fact, the standard model in the field of cancer treatment. The website for the National Cancer Institute focuses an entire section on mouse models. The NCI has a collaborative program, the NCI Mouse Models of Human Cancers Consortium (MMHCC), and sponsors a variety of other projects to "Develop, analyze and apply mouse cancer models." See the first page of the "e-mouse" portion of the NCI web site, a copy of which is attached. Also attached is the first page of the "Mouse Models" subsection of that portion of the site.

6. The effectiveness of complexes of our invention in treating human cancer cells has been shown with both antisense oligonucleotide and nucleic acid as the therapeutic molecule and several different liposome/ligand combinations. Enclosed with this Declaration and Amendment are several publications resulting from and describing work carried out in my laboratory which illustrates the effectiveness of our complexes. We have data

demonstrating *in vivo* systemic anti-cancer efficacy in a number of different tumor models, including head and neck cancer, breast cancer, prostate cancer, pancreatic cancer and bladder cancer.

7. In addition, our work has been recognized nationally and internationally. Dr. Edward Sausville (Director) and colleagues in the Developmental Therapeutic Division, National Cancer Institute (NCI) have reproduced our results. The NCI, through a number of peer-reviewed funding mechanisms and small business technology transfer grants, has been supporting our work and is, in collaboration with us, actively working on moving our delivery system into clinical trials. Our tumor-targeted delivery system will be used in two gene therapy clinical trials at both MD Anderson Cancer Center and the Georgetown Medical Center.

8. My co-inventors and I have been invited to give oral presentations on this invention and its efficacy in over twenty national and international meetings. In February, 2003, we presented our work at the request of the U.S. FDA at the 6th U.S.-Japan Cellular and Gene Therapy Conference. This further illustrates the regard held for and credibility accorded this invention.

9. One of the references cited by the examiner against the claims of this application is U.S. Patent 6,077,834. The examiner

asserted in the Office Action that it "necessarily would flow" from the teachings of this patent "that the cationic lipid/transferrin/DNA complexes after mixing and incubation must exhibit a mean diameter of less than 100 nm." This statement is not correct.

The '834 patent does not make any statements about the actual size of the complexes disclosed therein. Under my direction, experiments were carried out to determine if the size of complexes made in accordance with Example 1 of the patent. For these experiments, size was measured by laser Dynamic Light Scattering (DLS). As an initial step, we determined the size of complexes made in accordance with our invention and originally measured using the method described in Example 24 of our application. We found that using DLS, the size determination matched that determined using Negative staining and cryo electron microscope imaging as described in Example 24. By both methods particles made in accordance were found to have a relatively uniform size of less than 100 nm. The Zeta potential (a measure of the charge of the complex) of our complex is within the range of +25 to +35 mV.

Under my direction, a complex made following the teachings of Example 1 of the '834 patent was made three times. The

complexes were made using his preferred ratios of 1.5 µg DNA/ 3 µg lipofectin (a commercially available liposome)/ 32 µg transferrin (Tf), with the DNA and Tf in HBS and 15 minutes between additions. We saw the presence of a fine precipitate in the complex that was not seen when our complex was made. Size and Zeta potential were measured using a Malvern Zetasize 3000.

The cumulative mean size of the complex was found to vary from 207.8 to 376.8 nm, with a Polydispersity ranging from 0.453 to 0.895. By intensity, the size varied from 7.6 to 8810.4 nm, while the size by volume ranged from 8.1 to 5550.6 nm.

It is well known to one of skill in the art that a particle size in the range of 7 - 8 nm or so represents unincorporated lipids. Furthermore, the average mean size by intensity and volume over the several experiments were 336.9 and 453.9, respectively, clearly significantly above the 100 nm upper size limit of the complexes of our invention.

As noted above, the Polydispersity of the complexes was found to range from 0.453 to 0.895. The Polydispersity Index is a measure of the uniformity of the size of particles formed in solution. A Poly Index above 0.4 indicates an unacceptable level of size heterogeneity, that is, it indicates that there is a large variation in complex size in the final transfection solution. In

contrast, the complexes of our invention consistently are found to have a Poly Index between 0.2 and 0.3.

Also highly significant, the Zeta potentials for the complexes made in accordance with Example 1 of the '834 patent were in the range of -33.2 to -32.3, which indicates that the final complex has a large net negative charge and thus is anionic, not cationic as declared in the '834 patent.

Not only are these complexes quite different in size and in charge from those of our invention, they also are different in shape. The '834 patent refers to the DNA as being "complexed" with the lipofectin (col. 7, lines 6-7), and this is shown in diagrammatic fashion in Figure 4 of the patent. The patent states that the preferred structure for efficient transfection is that labeled as structure B, in which individual transferrin-lipofectin molecules are complexed to the DNA but the DNA is not encapsulated within one liposome particle with the targeting transferrin ligand on the surface as we describe in Example 24 of our application. Our complexes are essentially spherical, as shown in the electron microscopy images of Figure 5 of Xu, L., et al. *Human Gene Therapy* 13:469-481 (2002), enclosed with this Declaration and Amendment. The particle structure provided in Figure 4 of the '834 patent, therefore, are dramatically different from that of the present

invention.

These data indicate that contrary to the examiner's assertion, complexes made in accordance with the specific teachings of the '834 patent examples, are significantly different in size, shape and charge from those claimed in our application. The small spherical nanoparticle structure of the complexes of our invention plays a large role in the demonstrated *in vivo* targeting specificity and efficacy after systemic delivery of the complexes.

10. A final point I wish to make concerns a statement made in Example 17 of our application. In this Example, it is stated that some complexes made at a ratio of 1 µg DNA/ 12 nmoles liposome/ 15 µg transferrin might be toxic and/or precipitate. This statement was based upon one preliminary experiment. Further experiments using complexes having this ratio have shown that this is not the case. Complexes made by the method of our invention at this ratio did not precipitate and demonstrated no toxicity when used to transfect human pancreatic tumor cells.

11. I further declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true, and that these statements were made with the knowledge that wilful false statements and the like so made are punishable by fine or

imprisonment, or both, under Section 1001 of Title 18 of the United States Codes, and that such wilful false statements may jeopardize the validity of the application and any patent issuing thereon.

Esther Chang, Ph.D. Date 5/6/03

Esther H. Chang, Ph.D.
Professor, Department of Oncology and Otolaryngology
Georgetown University Medical Center

In addition to her faculty position at Georgetown University, Dr. Chang is a Consultant Professor in the Department of Surgery at Stanford University. Before joining Georgetown University, Dr. Chang held positions as a cancer expert for the National Cancer Institute (NCI), as a Professor in the Department of Pathology and Surgery at the Uniformed Services University of Health Sciences, and as a Professor in the Department of Surgery at Stanford University. She serves on the Board of Scientific Advisors for NCI and US Military Cancer Institute.

Research: Dr. Chang's efforts focus primarily on the molecular mechanisms of carcinogenesis. Delineation of the roles of various genetic factors in the multistep process of tumor formation is the key to improved diagnosis and effective therapy of cancer. Dr. Chang has been a contributor to the understanding of the effects of these genetic influences on many of the events leading to neoplasms. More recently, her research group has been evaluating the combination of systemic, tumor targeted gene therapy and more conventional radiotherapy or chemotherapy for treatment of cancers. She has written over 120 publications and has been appointed to a number of professional advisory boards. Her scientific papers, some of which were widely cited following their respective years of publication, have appeared in prominent journals such as *Nature*, *Science* and *Human Gene Therapy.*

PERSONAL

Name:	Esther H. Chang
Place of Birth:	Chungking, China
Citizenship:	U.S. Citizen
Marital Status:	Married with 1 daughter (Harford)
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Home Address:	7508 Vale Street Chevy Chase, MD 20815 Phone: (301) 913-5964 FAX: (301) 913-5284
Email Address:	change@georgetown.edu

EDUCATION

Fu Jen University, Taiwan	B.A.	1968	Biology
Southern Illinois University	Ph.D.	1974	Microbiology

PROFESSIONAL APPOINTMENTS

Trainee U.S. Naval Medical Research Unit No. 2 Taiwan	1967 - 1968
Research Assistant Southern Illinois University	1968 - 1971
Teaching Assistant in Immunology and Virology Southern Illinois University	1971 - 1972
Research Associate Southern Illinois University	1972 - 1973
Special Dissertation Fellow Southern Illinois University	1973 - 1974
Visiting Fellow National Institutes of Health	1974 - 1977
Visiting Associate National Institutes of Health	1977 - 1978
Cancer Expert National Cancer Institute	1978 - 1982
Assistant Professor Department of Pathology Uniformed Services University of the Health Sciences	1982 - 1983
Associate Professor and Coordinator for Medical Genetics Curriculum Department of Pathology	1983 - 1988

Uniformed Services University of the Health Sciences Professor, Department of Pathology Research Professor, Department of Surgery Coordinator for Medical Genetics Curriculum Director, Tumor Biology Program Uniformed Services University of the Health Sciences	1988 - 1994
Professor of Surgery (Research) Division of Otolaryngology/Head & Neck Surgery Department of Surgery Stanford University Medical Center	1994 - 1996
Professor of Surgery (Consultant) Division of Otolaryngology/Head & Neck Surgery Department of Surgery Stanford University Medical Center	1996-Present
Professor of Otolaryngology Department of Otolaryngology/Head & Neck Surgery Georgetown University Medical Center Lombardi Cancer Center	1996-Present
Professor of Oncology and Otolaryngology Departments of Oncology and Otolaryngology Georgetown University Medical Center Lombardi Cancer Center	1999-Present

HONORS AND OTHER SPECIAL RECOGNITION

Honor Society of Phi Kappa Phi	1972
Special Dissertation Fellow Southern Illinois University	1973 - 1974
Author, two papers in 100 most-cited papers in Life Sciences, Current Contents, November 5, 1984	1982 - 1983
Conference Organizer-International Conference on Molecular Biology of Neoplasia Taipai, Taiwan	1984
Ad Hoc Reviewer for NIH Study Section	1985
One of six awardees, Visiting Scholar Exchange Program, National Academy of Sciences, American Council of Learned Societies and Social Science Research Council	1986 - 1987
Member, Merit Review Committee, USUHS	1987 - 1989
Ad hoc Member, Review Panel for Assessment of Department of Energy research projects on chemical toxicology	1989
Member, Faculty Senate Education Committee, USUHS	1990 - 1991
Member, Editorial Board of Antisense Research and Development	1990 - Present
Member, Steering Committee on Prescribing of Drugs by Military Psychologists	1991

Chairman, Subcommittee for Faculty Resources for the Educational Program, Institutional Self-Study at USUHS	1991 - 1993
Member, Scientific Advisory Committee on Design Study for Life Span Experiments in Mice on Carcinogenesis and Biological Effects of Heavy Charged Particles, NASA	1992 - 1994
Chairman, Subcommittee to Examine Faculty, Middle States Association Reaccreditation Self-Study, USUHS	1992 - 1993
Ad hoc Member, Special Review Committee, Epidemiology, NCI	1992
Author, one Nature paper in top ten most cited papers in medicine Science Watch, September, 1992	1992
Member, Board of Scientific Counselors, Division of Cancer Biology, Diagnosis and Centers, National Cancer Institute	1993 - 1995
Member, NASA Life and Microgravity Sciences and Applications Advisory Committee	1994 - Present
Member, Interim ad hoc Board of Scientific Counselors, National Cancer Institute, NIH	1995 - 1996
Chair, Molecular Genetics Study Section, U.S. Army Breast Cancer Research Program	1997
Chair, Experimental Gene Therapy, Program Committee AACR Annual Meeting	1999
Member, Board of Scientific Advisors, National Cancer Institute	1999 - 2004
Member , Editorial Board of Cancer Gene Therapy	1999 - Present
Member, Scientific Program Committee. Chair, Gene Therapy Program NCI-EORTC-AACR Symposium	1999
Distinguished Alumni, Fu Jen University	1999
10th Lecturer, Stewart Lectureship	2000
Member, NASA Focus Group - National Academy of Sciences, Committee on Science, Engineering, and Public Policy	2000
Member, Committee of Scientific Advisors, United States Military Cancer Institute	2001 – Present
Ad hoc member, Experimental Therapeutics I + II, Study Section, NIH	2002
Organizer, Conference on "Tumor Specific Delivery by Non-Viral Systems" Maui, Feb. 2003 Sponsored by NCI	2002-2003
Approximately 10 annual invited lectures at national and international conferences and academic and research institutes	1982 - Present

DISSERTATION TITLE
Comparative Studies of Growth Patterns of Ganjam Virus in CE, BHK and VERO and *Aedes albopictus* Cells

RESEARCH ACTIVITIES
Undergraduate

Insect tissue culture. Studied growth pattern of insect line cells (Bombyx, Aedes and Antheraea) and adapted two lines into hemolymph-free media. Gained some experience in the growth of Japanese Encephalitis Virus in insect cells and newborn mice.

Graduate School

Arboviruses (Togaviruses). Electron microscopy. Compared the growth of VSV in insect cells and chicken embryo fibroblasts. Determined the viral RNA profiles in each cell line.

Characterized Ganjam Virus, an ungrouped arbovirus.

Postgraduate

RNA tumor viruses - interferon effect. Studied interferon's inhibitory effect on the replication of murine leukemia virus. (In Robert M. Friedman's laboratory, National Institutue of Arthritis, Metabolic and Digestive Diseases, NIH).

Molecular genetics. Cloned and characterized murine leukemia and sarcoma viruses. Investigated the origin and the functional organization of Harvey murine sarcoma virus. Molecularly cloned four DNA fragments containing human homologous sequences of v-*ras* (2 Harvey and 2 Kirsten) and demonstrated their oncogenic potentials. Studied potential human oncogenes. (In Douglas R. Lowy's Laboratory, Dermatology Branch, National Cancer Institute, NIH).

Current

1) Molecular genetic basis of familial cancer syndrome and the involvement of human oncogenes and tumor suppressor genes in carcinogenesis.
2) Modulation of oncogene expression by sequence-specific antisense oligonucleotides.
3) Molecular basis of cellular radioresistance and radioprotection.
4) Tumor Suppressor Gene Therapy for Cancer (Head and Neck, Breast and Prostate)
5) Ligand directed, tumor-targeted liposome-based systemic gene delivery

MEMBERSHIP IN ORGANIZATIONS AND PROFESSIONAL AFFILIATIONS

Honor Society of Phi Kappa Phi	1973-
American Association for the Advancement of Science	1983-
Society of Chinese Bioscientists in America	1988-
The Wound Healing Society	1991-
American Association for Cancer Research	1993-
American Society of Gene Therapy	1997-

PUBLICATIONS - ESTHER H. CHANG

1. R. M. Friedman, **E. H. CHANG**, J.M. Ramseur and M.W. Myers. Interferon-directed inhibition of chronic murine leukemia virus production in cell cultures: Lack of effect of intracellular viral markers. **J. Virol. 16**: 569-574 (1975).

2. R. M. Friedman, J.C. Costa, J.M. Ramseur, M.W. Myers, F.T. Jay and **E. H. CHANG**. Persistence of the viral genome in interferon-treated cells infected with oncogenic or nononcogenic viruses. **The J. Infectious Diseases 133**: A43-A50 (1976).

3. R. M. Friedman, F. T. Jay, **E. H. CHANG**, M. W. Myers, J. M. Ramseur, S. J. Mims, T. J. Triche, and P.K.Y. Wong. Interferon-directed inhibition of chronic murine leukemia virus production in cell cultures. In: Control of Neoplasia by Modulation of the Immune System. (M.A. Chirigos, ed.), Raven Press, New York (1977), pp. 347-359.

4. R. M. Friedman, E. F. Grollman, **E. H. CHANG**, L. D. Kohn, G. Lee and F. T. Jay. Interferon and glycoprotein hormones. In: Texas Reports on Biology and Medicine (1977), pp. 326-329.

5. R. M. Friedman and **E. H. CHANG**. Interferon action. Possible mechanisms of antiviral activity. In: Interferons and Their Actions (M. Stewart, ed.) CRC Handbook Series (1977), pp. 145-152.

6. **E. H. CHANG,** S. J. Mims, T. J. Triche, and R. M. Friedman. Interferon inhibits mouse leukemia virus release: An electron microscope study. **J. Gen. Viron. 34**: 363-367 (1977).

7. P. K. Y. Wong, P. H. Yuen, R. Macleod, **E. H. CHANG,** M. W. Myers, and R. M. Friedman. The effect of interferon on *de novo* infection of Moloney murine leukemia virus. **Cell 10**: 245-252 (1977).

8. **E. H. CHANG,** M. W. Myers, P. K. Y. Wong, and R. M. Friedman. The inhibitory effect of interferon on a temperature-sensitive mutant of Moloney murine leukemia virus. **Virology 77**: 625-636 (1977).

9. **E. H. CHANG,** and R. M. Friedman. A large glycoprotein of Moloney leukemia vrius derived from interferon-treated cells. **Biochem. Biophys. Res. Commun. 77:** 392-398 (1977).

10. **E. H. CHANG,** F. T. Jay and R. M. Friedman. Physical and morphological alteration in the membrane of AKR cells following interferon treatment and their correlation with the establishment of the antiviral state. **Proc. Natl. Acad. Sci. 75**: 1859-1863 (1978).

11. **E. H. CHANG**, E. F. Grollman, F.T. Jay, G. Lee, L. D. Kohn and R.M. Friedman. Membrane alterations following interferon treatment. In: Human interferon. W. Alton Jones Cell Science Center, Lake Placid, New York (1978), pp. 85-99.

12. A. K. Bandyopadhyay, **E. H. CHANG,** C. C. Levy and R. M. Friedman. Structura abnormalities in murine leukemia viruses produced by interferon-treated cells. **Biochem. Biophys. Res. Commun. 87**: 983-988 (1979).

13. G. L. Hager, **E. H. CHANG,** H. W. Chan, C. F. Garon, M. A. Israel, M. A. Martin, E. M. Scolnick and D. R. Lowy. Molecular cloning of the Harvey sarcoma virus closed circular DNA intermediates: Initial structural and biological characterization. **J. Virol. 31**: 795-809 (1979).

14. H. W. Chan, C. F. Garon, **E. H. CHANG**, D. R. Lowy, G. L. Hager, E. M. Scolnick, R. Repaske and M. A. Martin. Molecular cloning of the Harvey sarcoma virus circular DNA intermediates: II. Further structural analyses. **J. Virol. 33**: 845-855. (1980).

15. A. I. Oliff, G. L. Hager, **E. H. CHANG,** E. M. Scolnick, H. W. Chan and D. R. Lowy. Transfection of molecularly cloned Friend murine leukemia virus DNA yields a highly leukemogenic helper independent type C virus. **J. Virol. 33**: 475-486 (1980).

16. S. L. Berger, M. J. Hitchcock, K. C. Zoon, C. S. Birkenmeier, R. M. Friedman and **E. H. CHANG**. Characterization of interferon messenger RNA synthesis in namalva cells. **J. Biol. Chem. 255:** 2955-2961 (1980).

17. E. **H. CHANG**, J. Maryak, D. M. Wei, T. Y. Shih, R. Shober, H. L. Cheung, R. W. Ellis, G. L. Hager, E. M. Scolnick and D. R. Lowy. Functional organization of the Harvey murine sarcoma virus genome. **J. Virol. 35**: 76-92 (1980).

18. R. W. Ellis, D. DeFeo, J. M. Maryak, H. A. Young, T. Y. Shih, **E. H. CHANG,** D. R. Lowy and E. M. Scolnick. A dual evolutionary origin for the rat genetic sequences of Harvey murine sarcoma virus. **J. Virol. 36**: 408-420 (1980).

19. **E. H. CHANG** and D. R. Lowy. Transformation by molecularly cloned Harvey murine sarcoma virus DNA. **J. Supramol. Struc. 9 (Supp. 4)**: 237 (1980).

20. E. M. Scolnick, T. Y. Shih, J. Maryak, R. Ellis, **E. H. CHANG** and D. Lowy. Guanine neucleotide binding activity of *src* gene product of rat-derived murine sarcoma viruses. **Ann. N.Y. Acad. Sci. 354**: 398-409 (1980).

21. **E. H. CHANG**, R. W. Ellis, E. M. Scolnick and D. R. Lowy. Transformation by cloned Harvey murine sarcoma virus DNA: Efficiency increased by long terminal repeat DNA. **Science 210**: 1249-1251 (1980).

22. D. DeFeo, M. A. Gonda, H. A. Young, **E. H. CHANG**, D. R. Lowy, E. M. Scolnick and R. W. Ellis. Analysis of two divergent rat genomic clones homologous to the transforming gene of Harvey murine sarcoma virus. **Proc. Natl. Acad. Sci. 78**. 3328-3332 (1981).

23. D.R. Lowy, R.W. Ellis, D. DeFeo, **E. H. CHANG**, M.A. Gonda, H.A. Young, N. Tsuchida, T.Y. Shih and E.M. Scolnick. The cellular p21 sarc genes represent a family of divergent normal genes which have the capacity to transform mouse cells. In: RNA Tumor Viruses, New York, Cold Spring Harbor (1981), p. 294.

24. D.R. Lowy, R.W. Ellis, D. DeFeo, **E. H. CHANG**, M.A. Gonda, A. Young, T.Y. Shih and E.M. Scolnick. The family of cellular P21 sarc genes. In: Intl. Union of Microbiol. Soc., Virology Division (1981), p. 462.

25. **E. H. CHANG**, D.R. Lowy, M. Gonda, D. DeFeo, E.M. Scolnick and R.W. Ellis. The p21 gene family: Human and rodent DNA sequences homologous to the transforming genes of Harvey and Kirsten murine sarcoma viruses. In: Advances in Comparative Leukemia Research (1981), pp. 379-380.

26. D. R. Lowy. **E. H. CHANG**, R. W. Ellis, D. Defeo and E. M. Scolnick. Elevated levels of an evolutionarily conserved normal rat protein can induce cellular transformation. **Clin. Res. 29(2):** 428 (1981).

27. S. K. Chattapadhyay, **E. H. CHANG**, M. R. Lander, R. W. Ellis, E. M. Scolnick and D. R. Lowy. Selective amplification of *onc* genes in mammalian species. **Nature 296**: 361-363 (1982).

28. D. R. Lowy, **E. H. CHANG**, R. M. Ellis, M. A. Gonda, T. Shih, D. DeFeo and E. M. Scolnick. Harvey and Kirsten sarcoma viruses and the P-21 gene family. **J. Cell Biochem. Suppl. 6**: 194 (1982).

29. **E. H. CHANG**, M. A. Gonda, R. W. Ellis, E. M. Scolnick and D. R. Lowy. The human genome contains four genes homolgous to the transforming genes of Harvey and Kirsten murine sarcoma viruses. **Proc. Natl. Acad. Sci. 79**: 4848-4852 (182).

30. **E. H. CHANG**, M. A. Furth, E. M. Scolnick and D. R. Lowy. Tumorigenic transformation of mammalian cells induced by a normal human gene homologous to the oncogene of Harvey murine sarcoma virus. **Nature 297**: 497-483 (1982).

31. D. R. Lowy, M. A. Gonda, M. E. Furth, R. W. Ellis, E. M. Scolnick, and **E. H. CHANG.** Tumorigenic transformation of mammalian cells induced by elevated levels of a normal human *onc* protein. **Clin. Res. 30(2)**: 421 (1982).

32. C. J. Tabin, S. M. Bradley, C. L. Borgmann, R. A. Weinberg, A. G. Papageorge, E. M. Scolnick, R. Dhar, R. Lowy and **E. H. CHANG**. Mechanism of activation of a human oncogene. **Nature 300**: 143-149 (1982).

33. B. D. Crawford, **E. H. CHANG**, J. L. Goodwin, C. E. Hildebrand, P. M. Kraemer, J. L. Longmire and R. D. Palmiter. **J. Cell Biochem. Suppl. 7**: 135 (1983).

34. **E. H. CHANG**, M.A. Gonda, M.E. Furth, J.L. Goodwin, S.E. Yu, R.W. Ellis, E.M. Scolnick and D.R. Lowy. Characterization of four members of the p21 gene family isolated from normal human genomic DNA and demonstration of their oncogenic potential. In: Gene Transfer and Cancer, Raven Press, New York (1983), pp. 189-197.

35. **E. H. CHANG**, M.A. Gonda, E.M. Scolnick and D.R. Lowy. Characterization of 4 divergent human genomic clones homologenes to the transforming p21 genes of Harvey and KiMuSV. In: Gene to Protein--Translation into Biotechnology, American Press (1983), p. 512.

36. D.R. Lowy, M.A. Gonda, M.A. Furth, R.W. Ellis, E.M. Scolnick and **E. H. CHANG**. The human genes homologous to p21 *ras* viral oncogenes. In: Tumor Viruses and Differentiation, Alan R. Liss, Inc., (1983), pp. 435-444.

37. D. Samid, **E. H. CHANG** and R.M. Friedman. Revertants from interferon-treated mouse cells transformed by a human oncogene. In: The Biology of the Interferon System, Elsevier Science Publishers, (1983), pp. 359-360.

38. M. S. McCoy, J. J. Toole, J. M. Cunningham, **E. H. CHANG**, D. R. Lowy and R. A. Weinberg. Characterization of a human colon/lung carcinoma oncogene. **Nature 302**: 79-81 (1983).

39. S. J. O'Brien, W. G. Nash, J. L. Goodwin, D. R. Lowy and **E. H. CHANG**. Dispersion of the *ras* family of transforming genes to four different chromosomes in man. **Nature 302**: 839-842 (1983).

40. M. R. Pincus, J. van Reswoude, J. B. Harford, **E. H. CHANG** and R. D. Klausner. Prediction of the three-dimensional structure of the transforming region of the EJ/T24 human bladder oncogene product and its normal cellular homologue. **Proc. Natl. Acad. Sci. 80**: 5253-5257 (1983).

41. S. J. O'Brien, W. G. Nash, R. Bauer, **E. H. CHANG** and L. J. Seigel. Trends in chromosomal and oncogene evolution in vertebrates. "Uses and Standardization in Vertebrae Culture Cells" (M. K. Paterson, ed.), *IN VITRO* **Monograph No. 5**: Gaithersburg Tissue Culture Association (1984), pp. 204-214.

42. D. Samid, **E. H. CHANG** and R. M. Friedman. Biochemical correlates of reversion in interferon-treated mouse cells transformed by a human oncogene. **Biochem. Biophys. Res. Commun. 119:** 21-28 (1984).

43. D. Samid, **E. H. CHANG** and R. M. Friedman. Inhibition by interferon of transformation induced by a human *ras* oncogene. **Biochem. Biophys. Res. Commun. 126(1):** 509-516 (1985).

44. D. Samid, Z. Schaff, **E. H. CHANG** and R.M. Friedman. Reduction in *ras* expression accompanies phenotypic reversion of interferon-treated, c-Ha-*ras* oncogene transformed mouse cells. In: The Biology of the Interferon System (H. Kirchner and H. Shellekens, eds.), Elsevier, Amsterdam (1985), pp. 189-198.

45. D. Samid, Z. Schaff, **E. H. CHANG** and R. M. Friedman. Interferon-induced modulation of human *ras* oncogene expression. Endocoids. In: Progress in Clinical and Biological Research, Vol. 192 (H. Lal, F. La Bella and J. Lane, eds.), Alan R. Liss, New York (1985), pp. 265-268.

46. D. Samid, **E. H. CHANG** and R.M. Friedman. Specific inhibition by interferon of oncogene-induced transformation. In: Serono Symposia Publications, Vol. 24 (F. Dianzani and G.B. Rossi, eds.), Raven Press, New York, (1985), pp. 425-422.

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THESIS AND DISSERTATION

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2. **E. H. CHANG.** Comparative studies of growth patterns of Ganjam Virus in CE, BHK and VERO and *Aedes albopictus*cells. Ph.D. Dissertation, Southern Illinois University, Carbondale, Illinois (1974).

PATENT - APPLICATION FILED

1. c-Raf Transgenic Non-Human Mammals.
2. An Automated Method for the Detection of p53 Mutations.
3. Treatment of Tumors by a Combination of Radiation Therapy and Transduction with Polynucleotide Encoding Wild Type p53.
4. Method of Reversal of Resistance to Radiation Therapy and to Chemotherapy in Cancer Cells Using Sequence-Specific Anti-HER-2 Oligonucleotides.
5. Modified Antisense Nucleotides Complementary to a Section of the Human Ha-*ras* Gene.
6. Targeted Liposome Gene Delivery.
7. Compositions and Methods for Reducing Radiation and Drug Resistance in Cells.
8. Systemic Viral/Ligand Gene Delivery System and Gene Therapy.
9. Ligand-PEG "Post-coated" Cationic Liposomes for Targeted Gene Delivery.
10. Antibody Fragment-Targeted Immunoliposomes for Systemic Gene Delivery.
11. A Simplified and Improved Method for Complexing an Antibody Fragment-Targeted Immunoliposome for Systemic Gene Delivery.